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MOLLI and AIR T1 Mapping Pulse Sequences Yield Different Myocardial T1 and ECV Measurements

KyungPyo Hong1,2 and **Daniel Kim**²

¹Department of Bioengineering, University of Utah, Salt Lake City, UT, 84112

²UCAIR, Department of Radiology, University of Utah, Salt Lake City, UT, 84108

Abstract

Both post-contrast myocardial T1 and extracellular volume (ECV) have been reported to be associated with diffuse interstitial fibrosis. Recently, the cardiovascular magnetic resonance (CMR) field is recognizing that post-contrast myocardial T1 is sensitive to several confounders and migrating towards ECV as a measure of collagen volume fraction. Several recent studies using widely available Modified Look-Locker Inversion-recovery (MOLLI) have reported ECV cutoff values to distinguish between normal and diseased myocardium. It is unclear if these cutoff values are translatable to different T1 mapping pulse sequences such as arrhythmia-insensitive-rapid (AIR) cardiac T1 mapping, which was recently developed to rapidly image patients with cardiac rhythm disorders. We sought to evaluate, in well-controlled canine and pig experiments, the relative accuracy and precision, as well as intra- and inter-observer variability in data analysis, of ECV measured with AIR as compared with MOLLI.

In 16 dogs, as expected, mean T1 was significantly different $(p < 0.001)$ between MOLLI $(891\pm373 \text{ ms})$ and AIR $(1071\pm503 \text{ ms})$, but, surprisingly, mean ECV between MOLLI $(21.8\pm2.1\%)$ and AIR (19.6 \pm 2.4%) was also significantly different (p < 0.001). Both intra- and inter-observer agreements in T1 calculations were higher for MOLLI than AIR, but intra- and inter-observer agreements in ECV calculations were similar between MOLLI and AIR. In 6 pigs, coefficient of repeatability (CR), as defined by Bland-Altman analysis, of T1 was considerably lower for MOLLI (32.5 ms) than AIR (82.3 ms), and CR of ECV was also lower for MOLLI (1.8%) than AIR (4.5%).

In conclusion, this study shows that MOLLI and AIR yield significantly different T1 and ECV values in large animals and that MOLLI yields higher precision than AIR. Findings from this study suggest that CMR researchers must consider the specific pulse sequence when translating published ECV cutoff values into their own studies.

Keywords

Diffuse myocardial fibrosis; post-contrast myocardial T_1 ; extracellular volume fraction; CMR; T1 mapping

Please send correspondence to: Daniel Kim, The University of Utah, 729 Arapeen Drive, Salt Lake City, Utah 84108, Phone: (801) 587-3861, Fax: (801) 585-3592, daniel.kim@hsc.utah.edu.

Introduction

Diffuse myocardial fibrosis is a marker of adverse structural remodeling in a variety of heart diseases. While myocardial biopsy is the current gold standard for assessment of diffuse cardiac fibrosis, it is rarely clinically indicated due to its associated non-negligible risk of complications and sensitivity to sampling errors. Cardiovascular magnetic resonance (CMR) is the only proven non-invasive modality for quantifying diffuse myocardial fibrosis. Both post-contrast myocardial T1 (1–4) and myocardial extracellular volume (ECV) fraction (4– 8), derived from native and post-contrast myocardial and blood T1 measurements, have been associated with diffuse interstitial fibrosis burden. These promising developments and findings are establishing the foundation towards non-invasive myocardial biopsy with CMR (9).

Among several different cardiac T1 mapping pulse sequences reported in literature (10–19), modified Look-Locker Inversion-recovery (MOLLI)(10) is the most widely used and commercially available as a work-in-progress. While MOLLI has been an important development in CMR, it requires a long scan time (17 heart beats) and is known to be sensitive to rapid heart rate and arrhythmia (20,21), T2 and magnetization transfer effects (19), and inversion pulse efficiency (22,23). These limitations are particularly concerning for imaging patients with irregular heart rhythm and/or rapid rates (e.g., atrial fibrillation). In response, we developed an arrhythmia-insensitive-rapid (AIR) cardiac T1 mapping pulse sequence (15) based on transmit radio-frequency field (B_1+) -insensitive saturation-recovery of magnetization preparation (24), in order to enable accurate cardiac T1 mapping in patients with rapid heart rate and/or arrhythmia. Because AIR cardiac T1 mapping is relatively new, reports of its performance are limited to a few preliminary studies (15,25– 27).

Recently, the CMR field is recognizing that post-contrast myocardial T1 is sensitive to confounders such as renal function, hematocrit, magnetic field strength, contrast agent type and dosage, and specific delayed imaging time after administration of contrast agent. Hence, the CMR field is migrating towards ECV, because it is largely insensitive to such confounders. Several recent studies using MOLLI have reported ECV cutoff values to distinguish between normal and diseased myocardium (4,28–30). It is unclear if these cutoff values are translatable to different T1 mapping pulse sequences such as AIR and others. This is especially important since other studies have reported that inversion-recovery based T1 mapping pulse sequences produce lower accuracy but higher precision than saturationrecovery based T1 mapping pulse sequences (31). As an important step towards clinical and pre-clinical utility of AIR, it is necessary to determine whether AIR and MOLLI yield comparable myocardial ECV (i.e., determine if ECV cutoff values established by MOLLI are translatable to AIR). The purpose of this study was to evaluate, in well-controlled canine and pig experiments, the relative accuracy and precision, as well as intra- and inter-observer variability in data analysis, of ECV measured with AIR as compared with MOLLI.

Experimental

MRI Hardware

CMR was performed on two 3T whole-body MRI scanners (Verio and Tim Trio, Siemens Healthcare, Erlangen, Germany), each equipped with a gradient system capable of achieving a maximum gradient strength of 45 mT/m and a slew rate of 200 T/m/s. The radio-frequency excitation was performed using the body coil. The pig experiments were performed on the Tim Trio MRI scanner with standard receiver coil arrays (typically 12-elements total). Canine experiments were performed on the Verio MRI scanner with a 32-element cardiac coil array (RAPID MR International, Columbus, OH).

Pulse Sequence

We used the MOLLI (Siemens WIP # 448) and AIR cardiac T1 mapping pulse sequences with balanced steady-state of free precession (b-SSFP) readout and the following identical set of imaging parameters: field of view = 280 mm \times 210 mm (phase-encoding), image acquisition matrix = 192×144 (phase-encoding), spatial resolution = 1.5 mm \times 1.5 mm, slice thickness $= 8$ mm, generalized autocalibrating partially parallel acquisitions (GRAPPA)(32) acceleration factor 1.8, TR = 2.7 ms, TE = 1.1 ms, flip angle = 35° , receiver bandwidth = 930 Hz/pixel, saturation-recovery time delay (TD) = 600 ms, and temporal resolution $= 217$ ms.

Figure 1 shows pulse sequence diagrams of AIR and MOLLI. Briefly, AIR acquires one proton-density weighted image and one T1 weighted image with breath-hold duration $= 2-3$ heart beats (depending on heart rate). MOLLI acquires 11 T1 weighted images following three inversion pulse modules (3-3-5, as shown). In this study, for AIR, we used "paired" consecutive phase-encoding steps in centric k-space ordering to minimize b-SSFP artifacts arising from eddy currents (33) . For MOLLI with breath-hold duration = 17 heart beats, we used the inversion times (i.e., 3-3-5) and flip angle of 35 as previously described (34).

Animal Subjects

Animal MRI was performed in accordance with protocols approved by our Institutional Animal Care and Use Committee. We note that this CMR study was added onto separate canine and pig CMR experiments, and that cardiac tissues were not made available for histolic analysis. We note that pig experiments were conducted after the canine experiments were completed, in order to acquire additional data for analysis of precision (i.e., since repeated measurements were not made in canines). For both canine and pig experiments, animals were anesthetized with propofol (5–8 mg/kg, IV) for intubation and subsequently ventilated and maintained in a surgical plane of anesthesia with 1.5–3% isoflurane. Ventilation was controlled using a ventilator (DRE Premier XP MRI-Compatible Veterinary Anesthesia Machine, DRE Veterinary, Louisville, KY). Breath-hold CMR image acquisitions were performed at end-expiration with the respirator suspended. Heart rate, core body temperature, blood pressure, end-tidal $CO₂$, and oxygen saturation were continuously monitored and maintained within normal ranges. Blood was drawn during the CMR exam for hematocrit calculation.

Experiment 1: Evaluation of Relative Accuracy in Canines

We imaged 16 mongrel dogs with normal myocardium (8 males and 8 females; 29.9 ± 4.2) kg) to assess the agreement of myocardial T1 and ECV measurements between MOLLI and AIR. In each dog, we performed native cardiac T1 mapping and post-contrast cardiac T1 mapping in a mid-ventricular short-axis plane during steady-state equilibrium of gadobenate dimeglumine (Gd-BOPTA)(Multihance, Bracco Diagnostics Inc., Princeton, NJ; ~45 min after slow infusion at 0.002 mmol/kg/min). This slow infusion rate was determined empirically based on our extensive experience with large animal (dogs, goats, pigs) CMR experiments. Note that steady-state equilibrium ensures identical concentration of Gd-BOPTA throughout repeated MRI measurements and allows for a fair comparison of postcontrast myocardial and blood T1 measurements by two different pulse sequences. Furthermore, by performing CMR during equilibrium, the specific pulse sequence order was irrelevant.

Experiment 2: Evaluation of Relative Precision in Pigs

Following the completion of separate canine experiments, we conducted an additional experiment to evaluate the precision of AIR compared with MOLLI. Specifically, we imaged 6 female pigs (mean weight = 50 ± 1.4 kg) with normal myocardium to assess scanto-scan repeatability of MOLLI and AIR. Similar to the canine experiment, in each pig, we performed native cardiac T1 mapping and post-contrast cardiac T1 mapping in a midventricular short-axis plane during steady-state equilibrium of Gd-BOPTA. MOLLI and AIR T1 mapping acquisitions were repeated to quantify scan-to-scan repeatability.

Image Analysis

MOLLI T1 maps were generated in-line on the MRI scanner (Siemens WIP # 448). AIR T1 maps were generated off-line as described in reference (15). Customized software in MATLAB (R2009a, MathWorks, Inc., Natick, MA) was used to manually segment the myocardial contours and blood pools in the left ventricle for each data set separately. Care was taken to avoid partial volume averaging for each contour tracing. T1 was calculated for AIR (15) and MOLLI (10) according to their corresponding equation. Myocardial and blood T1 values were averaged within their respective region of interest. Myocardial ECV was calculated as (35): ECV = (1–hematocrit) × ($R1_m/R1_b$) × 100%, where $R1_m$ is T1⁻¹ of myocardium, and $R1_b$ is $T1^{-1}$ of blood, and is the difference between post-contrast and native.

To assess the impact of data quality on analysis, we assessed intra- and inter-observer variability in calculation of T1 and ECV (canine data only). For assessment of intra-observer variability, one observer (K.H) repeated the image analysis, with at least two weeks of separation from the first analysis. For assessment of inter-observer variability, the second observer (D.K) independently analyzed the data. The two observers were blinded to each other, pulse sequence type, and animal identity.

Statistical Analysis

For canine data, we performed a pair-wise t-test to compare T1 and ECV between MOLLI and AIR. We also performed linear regression, concordance correlation (which accounts for

the intercept or additive bias), and Bland-Altman analyses on cardiac T1 and ECV measurements to assess correlation and agreement between MOLLI and AIR data. For assessment of intra- and inter-observer variability, the Bland-Altman analysis was performed on T1 and ECV measurements. A *p*-value < 0.05 was considered statistically significant.

For pig data, we performed Bland-Altman analysis on myocardial T1 and ECV to calculate the coefficient of repeatability (CR), which is defined as $1.95 \times$ standard deviation of the difference. To avoid confusion with terminology, we note that CR increases with variability in repeated measurements (i.e., higher agreement). All statistical analyses were performed using the Analyse-it software (Analyse-it Software, Ltd., Leeds, United Kingdom).

Results

Experiment 1: Evaluation of Relative Accuracy in Canines

Figure 2 shows representative native and post-contrast MOLLI and AIR cardiac T1 maps of one dog, illustrating typical image quality with both acquisitions. As expected, MOLLI T1 maps derived from 11 images exhibited better overall signal-to-noise ratio (SNR) than AIR T1 maps derived from only 2 images. In this dog (heart rate = 95 bpm), MOLLI and AIR cardiac T1 mapping pulse sequences yielded different T1 and ECV values (see Figure 2 caption for more details).

In 16 dogs (mean heart rate = 98.8 ± 17.5 bpm; mean hematocrit = 0.42 ± 0.02), as expected, mean T1 was significantly different ($p < 0.001$) between MOLLI (891 \pm 373 ms) and AIR $(1071 \pm 503 \text{ ms})$, but, surprisingly, mean ECV between MOLLI $(21.8 \pm 2.1 \text{ %})$ and AIR (19.6 \pm 2.4%) was also significantly different (p < 0.001). Pair-wise t-test revealed significant differences for all pairs ($p < 0.0001$), except for post-contrast blood T1 ($p = 0.55$; Table 1). Figure 3 shows scatter plots representing the linear regression and Bland-Altman analyses on T1 and ECV between MOLLI and AIR acquisitions. According to the linear regression and concordance correlation analyses, T1 values were strongly correlated (Pearson's correlation coefficient = 0.99, slope = 1.33, bias = −117.6 ms, *p* < 0.0001; concordance correlation coefficient $= 0.87$). According to the Bland-Altman analysis, the mean difference in T1 was 179 ms (\pm 95% confidential interval (CI) = 468/-109 ms), which corresponds to 18% of the mean T1 value (981 ms). According to the linear regression analysis, ECV values were moderately correlated (Pearson's correlation coefficient $= 0.65$, slope $= 0.77$, bias $= 2.8\%$, $p < 0.001$). According to the concordance correlation analysis, ECV values were weakly correlated (correlation coefficient $= 0.43$). According to the Bland-Altman analysis, the mean difference in ECV was -2.2% (± 95% CI = 1.5/ -5.9%), which corresponds to 10.8% of the mean ECV value (20.7%).

Experiment 2: Evaluation of Relative Precision in Pigs

Consistent with canine data, in 6 pigs (mean heart rate $= 78.1 \pm 12.1$ bpm; mean hematocrit $= 0.30 \pm 0.04$), mean T1 was significantly different (p < 0.01) between MOLLI (899.0 \pm 462.8 ms) and AIR (1051.2 \pm 635.0 ms), and mean ECV was significantly different also (p < 0.05) between MOLLI (25.6 \pm 3.1%) and AIR (20.7 \pm 1.6%). CR of T1 was considerably

lower for MOLLI (32.5 ms) than AIR (82.3 ms), and CR of ECV was also lower for MOLLI (1.8%) than AIR (4.5%). Recall that, according to the Bland-Altman analysis, lower CR means lower variability (i.e., higher agreement).

Evaluation of Intra- and Inter-Observer Variability in Analysis

For T1 calculations (Figure 4), the intra-observer agreements for MOLLI and AIR data sets were 0.6 ms (upper/lower 95% limits of agreement = 5.3/−4.0 ms) and 0.4 ms (upper/lower 95% limits of agreement = 9.2/−8.5 ms), respectively. These correspond to CR of 4.7 and 8.8 ms for MOLLI and AIR, respectively. The corresponding inter-observer agreements for T1 derived from MOLLI and AIR data sets were 0.009 ms (upper/lower 95% limits of agreement = 9.8/−9.8 ms) and 0.4 ms (upper/lower 95% limits of agreement = 22.7/−21.9 ms), respectively. These correspond to CR of 9.8 and 22.3 ms for MOLLI and AIR, respectively.

For ECV calculations (Figure 5), the intra-observer agreements for MOLLI and AIR data sets were −0.09% (upper/lower 95% limits of agreement = 0.5/−0.7%) and 0.02% (upper/ lower 95% limits of agreement = 0.5/−0.4%), respectively. These correspond to CR of 0.6 and 0.5% for MOLLI and AIR, respectively. The corresponding inter-observer agreements for ECV derived from MOLLI and AIR data sets were −0.2% (upper/lower 95% limits of agreement = $1.1/-1.6%$) and $-0.1%$ (upper/lower 95% limits of agreement = $1.4/-1.6%$), respectively. These correspond to CR of 1.3 and 1.5% for MOLLI and AIR, respectively.

Discussion

In this study, we evaluated, in well-controlled canine and pig experiments, the relative accuracy and precision, as well as intra- and inter-observer variability in data analysis, of T1 and ECV measured with AIR as compared with MOLLI. Canine experiments showed that MOLLI and AIR yield significantly different T1 and ECV values ($p < 0.001$), which have important implications (see below). Both intra- and inter-observer agreements in T1 calculations were higher for MOLLI than AIR, owing to the fact that MOLLI acquires 9 more images than AIR. Interestingly, both intra- and inter-observer agreements in ECV calculations were similar between MOLLI and AIR, possibly owing to off-setting errors when calculating ECV from multiple measurements (native and post-contrast myocardial and blood T1s). Pig experiments showed that MOLLI yields higher precision than AIR, which was expected since AIR acquires 9 less images than MOLLI.

Our observation has important implications for the CMR community. Currently, there are several different variants of inversion-recovery (10,11) and saturation-recovery (12–14,16) based cardiac T1 mapping pulse sequences, as well as a hybrid inversion- and saturationrecovery cardiac T1 mapping pulse sequence (17) and the "TI" scout sequence (18), which is commonly used in conjunction with late gadolinium enhanced MRI (36,37). These different pulse sequences may yield not only different T1 measurements but also ECV measurements, as reported in this study. This implies that CMR researchers must consider the specific pulse sequence when translating published ECV cutoff values into their own studies. It also implies that the CMR community must work towards standardizing cardiac T1 and ECV mapping protocols, in order to move the field forward and increase

reproducibility. The 2013 Society for Cardiovascular Magnetic Resonance and CMR Working Group of the European Society of Cardiology consensus statement (38) is one important step in the right direction towards protocol standardization.

This study has several limitations worth noting. First, we did not test different variants of MOLLI (34,39), because our group has the most experience with the original version of MOLLI (i.e., 3-3-5) that was provided by Siemens. Another study is warranted to test the performance of different variants of MOLLI. Second, we did not compare other inversionrecovery and saturation-recovery based cardiac T1 mapping pulse sequences (11– 14,17,18,40). Therefore, our observations may not be directly applicable for other pulse sequences not evaluated in this study. Our study adds to the growing list of studies which compare the performances of different cardiac T1 mapping pulse sequences (11,15,19,41,42). Third, the canines included in this study had a mean heart rate of 98.8 bpm, and pigs had a mean heart rate of 78.1 bpm. This implies that our observation may not be directly applicable for different heart rates and rhythm conditions. Fourth, the animals in this study did not have a prior history of heart disease (assumed to have normal myocardium and supported by ECV measurements). Therefore, our observations may not be directly applicable for hearts with focal and/or diffuse cardiac fibrosis, which changes post-contrast myocardial T1 and ECV values. Fifth, this study did not compare the accuracy of ECV measurements by MOLLI and AIR to histologic quantification of collagen volume fraction. A future study including comprehensive histologic evaluation is warranted to compare the accuracy of ECV measurements between MOLLI and AIR.

In conclusion, this study shows that MOLLI and AIR yield significantly different T1 and ECV values in large animals and that MOLLI yields higher precision than AIR. Both intraand inter-observer agreements in calculation of T1 were higher for MOLLI than AIR, but intra- and inter-observer agreements in calculation of ECV were similar between MOLLI and AIR. Findings from this study suggest that CMR researchers must consider the specific pulse sequence when translating published ECV cutoff values into their own studies.

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List of Abbreviations

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Figure 1.

Schematic of AIR (top row) and (bottom) MOLLI cardiac T1 mapping pulse sequences. AIR acquires one proton density and one T1-weighted image in succession with scan time of 2–3 heart beats, depending on heart rate as shown. MOLLI acquires 11 images with scan time of 17 heart beats, following three inversion pulses as shown (i.e., 3-3-5).

Figure 2.

Representative cardiac T1 maps of one dog (heart rate = 94.5 bpm) acquired with MOLLI (left) and AIR (right) cardiac T1 mapping pulse sequences: native (top row) and postcontrast (bottom row). These examples illustrate typical image quality produced by MOLLI and AIR. Compared with AIR T1 maps derived from only 2 images, MOLLI T1 maps derived from 11 images exhibited higher overall SNR. Native myocardial and blood T1 values were different (native myocardial T1 was 1074.1 ms (MOLLI) and 1373.4 ms (AIR); native blood T1 was 1492.7 ms (MOLLI) and 1692.9 ms (AIR). Post-contrast myocardial T1 was also different (605.5 ms [MOLLI] and 724.5 ms [AIR]), but post-contrast blood T1 was not different (389.2 ms [MOLLI] and 384.8 ms [AIR]). These differences in T1 resulted in discordant ECV measurements (22.0% and 18.8% for MOLLI and AIR, respectively).

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Figure 3.

Scatter plots representing linear regression (left column) and Bland-Altman (right column) analyses: T1 (top row) and ECV (bottom row) derived from MOLLI and AIR cardiac T1 mapping pulse sequences in 16 dogs. According to the linear regression and concordance correlation analyses, T1 values were strongly correlated (Pearson's correlation coefficient = 0.99, slope = 1.33, bias = −117.6 ms, *p* < 0.0001; concordance correlation coefficient = 0.87). According to the Bland-Altman analysis, the mean difference in T1 was 179 ms $(±$ 95% confidential interval (CI) = $468/-109$ ms), which corresponds to 18% of the mean T1 value (981 ms). For ease of interpretation, the Bland-Altman plot for T1 was displayed with y-axis ranging from −1000 to 1000 ms (i.e., approximately −100 to 100 % of the mean value of 981 ms). According to the linear regression analysis, ECV values derived were

moderately correlated (Pearson's correlation coefficient = 0.65 , slope = 0.77 , bias = 2.8% , *p* < 0.001). According to the concordance correlation analysis, ECV values were weakly correlated (correlation coefficient $= 0.43$). According to the Bland-Altman analysis, the mean difference in ECV was −2.2% (± 95% CI = 1.5/−5.9%), which corresponds to 10.8% of the mean ECV value (20.7%). For ease of interpretation, the Bland-Altman plot for ECV was displayed with y-axis ranging from −8 to 8% (i.e., approximately −10 to 10 % of the mean value of 20.7%). Difference defined as AIR - MOLLI.

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Figure 4.

Scatter plots representing the intra- (top row) and inter-observer (bottom row) agreements in calculation of T1 derived from MOLLI (left column) and AIR (right column) data sets. For intra-observer agreement, the mean difference in T1 was 0.6 ms (upper/lower 95% limits of agreement = 5.3/−4.0 ms) and 0.4 ms (upper/lower 95% limits of agreement = 9.2/−8.5 ms) for MOLLI and AIR, respectively. For inter-observer agreement, the mean difference in T1 was 0.009 ms (upper/lower 95% limits of agreement = 9.8/−9.8 ms) and 0.4 ms (upper/lower 95% limits of agreement = 22.7/−21.9 ms) for MOLLI and AIR, respectively. Note that CR was lower MOLLI than AIR, suggesting higher overall SNR for MOLLI than AIR. For ease of interpretation, the Bland-Altman plots were displayed with y-axis ranging from −50 to 50

ms (i.e., approximately −5 to 5 % of the mean value of 1000 ms). Solid and dotted lines represent the mean difference and 95% confidence intervals, respectively.

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Figure 5.

Scatter plots representing the intra- (top row) and inter-observer (bottom row) agreements in calculation of ECV derived from MOLLI (left column) and AIR (right column) data sets. For intra-observer agreement, the mean difference in ECV was −0.09% (upper/lower 95% limits of agreement = $0.5/-0.7%$) and $0.02%$ (upper/lower 95% limits of agreement = 0.5/−0.4%) for MOLLI and AIR, respectively. For inter-observer agreement, the mean difference in ECV was −0.2% (upper/lower 95% limits of agreement = 1.1/−1.6%) and −0.1% (upper/lower 95% limits of agreement = 1.4/−1.6%) for MOLLI and AIR, respectively. Note that CR was similar between MOLLI and AIR, possibly due to off-setting errors from multiple measurements. For ease of interpretation, the Bland-Altman plots were

displayed with y-axis ranging from −4 to 4% (i.e., approximately −5 to 5 % of the mean value of 20%). Solid and dotted lines represent the mean difference and 95% confidence intervals, respectively.

Table 1

Pair-wise t-test statistics comparing the different subgroups of T1 derived from MOLLI and AIR cardiac T1 mapping pulse sequences: native myocardial T1, native blood T1, post-contrast myocardial T1, and postcontrast blood T1. T1 value represents mean ± standard deviation.

